

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:) Examiner: Kemmerer, Elizabeth
)
David Botstein, et al.) Art Unit: 1646
)
Application Serial No. 09/992,643) Confirmation No: 4960
)
Filed: November 14, 2001) Attorney's Docket No. 39780-2730 PIC13
)
For: **SECRETED AND TRANSMEMBRANE**) **Customer No. 77845**
POLYPEPTIDES AND NUCLEIC ACIDS)
ENCODING THE SAME)
)

FILED VIA EFS ON August 12, 2008

ON APPEAL TO THE BOARD OF PATENT APPEALS AND
INTERFERENCES APPELLANTS' REPLY BRIEF

MAIL STOP APPEAL BRIEF - PATENTS

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

On October 12, 2007, the Examiner made a Final rejection to pending Claims 119-126 and 129-131. A Notice of Appeal was filed on January 14, 2008 and an Appellants' Appeal Brief was subsequently filed April 14, 2008.

An Examiner's Answer was mailed on June 12, 2008. The following constitutes Appellants' Reply Brief in response to the Examiner's Answer. This Reply Brief is accompanied by a Request for Oral Hearing.

ARGUMENTS

I. *Claim Rejections Under 35 U.S.C. §101 and §112, First Paragraph*

Concerning the rejection of Claims 119-126 and 129-131 under 35 U.S.C. §101 as allegedly lacking a specific, substantial and credible asserted utility or a well established utility, in his Answer, the Examiner cites the following arguments:

(1) The instant rejections are primarily based on whether or not genomic DNA levels (as measured by the gene amplification assay) correlate with either mRNA levels or polypeptide levels. The Examiner asserts that the Goddard declaration is insufficient to overcome the rejection because “while [it] speaks to the utility and enablement of genes, it does not speak to whether or not the encoded polypeptides are also found at increased levels in cancerous tissues.” (Examiner’s Answer, page 22) The Examiner addresses the pooled blood controls used in the gene amplification assay and asserts that the controls were not matched, non-tumor lung samples, but rather pooled DNA samples from blood of healthy subjects. The Examiner further asserts that “the significance can be questioned based on the strength of opposing evidence. In the instant case, the data were not corrected for aneuploidy and the controls used were not matched, non-tumor lung samples...” (page 21 of Examiner’s Answer).

(2) The Examiner alleges that the Ashkenazi declaration actually supports the Examiner’s position in that it “contradicts the assertion of utility in the specification, wherein the specification indicates that gene amplification is associated with protein over-expression but Dr. Ashkenazi indicates that this is not always the case.” (page 34 of the Examiner’s Answer).

(3) The Examiner asserts that references such as Pennica *et al.*, Konopka *et al.*, Hanna *et al.*, Sen *et al.*, Hittelman *et al.*, Fleischhacker *et al.*, Godbout *et al.*, and Li *et al.* constitute strong opposing evidence for the claimed polypeptides having utility and enablement, based on the presumption that the claimed polypeptides are also overexpressed following gene amplification (pages 16-17 of the Examiner’s Answer). Referring to the references by Sen, Fleischhacker and Hittelman, the Examiner alleges that, in general, non-cancerous epithelial tissues are frequently aneuploid, and thus an increase in genomic DNA is not diagnostic of cancer (pages 8-10 of the Examiner’s Answer). The Examiner also quotes Godbout as stating: “*It is generally accepted that co-amplified genes are not over-expressed unless they provide a*

selective growth advantage to a cell..." and thereby inquires whether Appellant can show evidence for PRO1112 providing a selective growth advantage to a cell (pages 11-12 of Examiner's Answer).

(4) Regarding the supportive references Orntoft *et al.*, Hyman *et al.* and Pollack *et al.*, made of record by the Appellants, and which clearly address gene amplification, the Examiner considers them flawed. The reasons cited were: Orntoft *et al.* only compared levels of about 40 well-resolved and focused on abundant proteins; Hyman *et al.* found 44% of highly amplified genes showed overexpression at the mRNA level, and 10.5% of highly overexpressed genes were amplified and even at this level of high amplification and high overexpression, the two did not correlate; Pollack *et al.* is also limited to highly amplified genes and used a different method to evaluate their results (pages 25-26 of Examiner's Answer).

Appellants strongly disagree with each of the Examiner's arguments on a number of grounds. The Examiner's arguments will be addressed in the order they are listed above.

Reply to the Examiner's arguments

(1) The Goddard Declaration was presented to show what ΔCt values were considered significant in the TaqMan™ assay. The ΔCt values for the DNA that encodes for PRO1112 showed **2.092 – 4.807 fold** amplification in **twelve** different colon tumors and **2.196 – 3.364 fold** amplification in **seven** lung tumors, which would be considered significant according to the Goddard Declaration. While this declaration addresses DNA values, it has been presented in this polypeptide case in conjunction with several other supportive references like Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, Bea *et al.*, Godbout *et al.*, etc. As explained previously, Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* were presented to show that in general, gene amplification increases mRNA expression. In addition, Appellants presented two Polakis Declarations (Polakis I and II) to show that, in general, mRNA levels correlate well with protein levels, and the Examiner seems to agree with this point especially in view of the recent Board Decision (Decision on Appeal No. 2006-1469) addressing microarray cases. Presentation of the Goddard Declaration is indeed relevant in this polypeptide case, because it forms a critical piece of evidence in this case. When placed together with the entire evidence presented for PRO1112, one would logically come to the conclusion that, it is more likely than not, that increased DNA

levels generally correlate well with increased mRNA levels (based on, for example, the teachings of supportive references like Orntoft et al., Hyman et al., Pollack et al., Bea et al., Godbout et al., etc.), and further, increased mRNA levels generally correlate well with increased protein levels (the two Polakis Declarations and the recent Board decision). In summary, just as in the microarray cases, Appellants have presented multiple pieces of evidence, such as the Goddard Declaration, the Ashkenazi Declaration, two Polakis Declarations, several references addressing the relationship between DNA and mRNA/ protein levels, etc., each of which is critical evidence that supports Appellants' position that PRO1112 polypeptides have utility based on the gene amplification results. Therefore, Appellants believe that a sound case has been presented for utility of PRO1112 as a diagnostic marker, based on the gene amplification data of its corresponding gene in the specification.

Further, the Examiner is required to view the statements in the declaration with the total evidence presented in this case. The case law has clearly established that in considering affidavit evidence, the Examiner must consider all of the evidence of record anew (*In re Rinehart*, 531 F.2d 1084, 189 USPQ 143 (C.c.P.A. 1976); *In re Piasecki*, 745 F.2d. 1015, 226 USPQ 881 (Fed. Cir. 1985)). "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument." (*In re Alton*, 37 USPQ2d 1578, 1584 (Fed. Cir. 1996) (quoting *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992)). Furthermore, the Federal Court of Appeals held in *In re Alton*, "We are aware of no reason why opinion evidence relating to a fact issue should not be considered by an Examiner (*In re Alton, supra*). Appellants also respectfully draw the Examiner's attention to the Utility Examination Guidelines (Part II.B. 66 Fed. Reg. 1098 (2001)) which state, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." Appellants submit that the Patent Office has failed to provide substantial evidence for disregarding the Goddard Declaration.

Regarding the rejection of pooled controls (addressed in the Goddard Declaration). Appellants respectfully point out that Pennica *et al.*, cited by the Examiner, teaches the exact

same "pooled normal blood controls" as that used in the instant gene amplification assay (for instance, see page 14718, column 1 and Figure 5 of Pennica *et al.*). Further, the references Bieche *et al.* and Pitti *et al.*, submitted as Exhibits F and G with the Goddard Declaration, also used "pooled normal blood controls" as control. For instance, in Pitti *et al.* the authors used the same quantitative TaqMan PCR assay and pooled normal blood controls described in the instant specification, to study gene amplification in lung and colon cancer of DcR3, a decoy receptor for Fas ligand. Pitti *et al.* analyzed DNA copy number "in genomic DNA from 35 primary lung and colon tumors, relative to pooled genomic DNA from peripheral blood leukocytes (PBL) of 10 healthy donors." (Page 701, col. 1). The authors also analyzed mRNA expression of DcR3 in primary tumor tissue sections and found tumor-specific expression, confirming the finding of frequent amplification in tumors, and confirming that the pooled blood sample was a valid negative control for the gene amplification experiments. In Bieche *et al.*, the authors used the quantitative TaqMan PCR assay to study gene amplification of myc, cend1 and erbB2 in breast tumors. As their negative control, Bieche *et al.* used normal leukocyte DNA derived from a small subset of the breast cancer patients (page 663). The authors note that "the results of this study are consistent with those reported in the literature" (page 664, col. 2). Thus, contrary to the Examiner's allegations, Pennica *et al.*, Pitti *et al.* and Bieche *et al.* in fact, confirm the validity of use of the "pooled blood control" as a negative control, and indicate that this control was widely utilized in the art at the time of filing of the instant application. Applicants further submit that the Examiner's position is scientifically incorrect because the instant application relies on **genomic DNA** amplification for utility and not cDNA expression. Different types of cells from the same organism should have the same set of genomic DNA. Thus, it does not matter what kind of cells you use for the control as long as the control cells have the entire genome. Accordingly, a "tissue-matched" control is not necessary in the gene amplification assay.

Regarding the art exemplified by Sen *et al.*, Fleischhaacker *et al.*, and Hittelman *et al.*, Appellants maintain their position that these references still support their case for the reasons outlined in their Appeal Brief filed April 14, 2008, which is hereby incorporated by reference. Briefly Appellants maintain that, even if the amplification of the PRO1112 gene were due to chromosomal aneuploidy (which Appellants expressly do not concede to), since there is utility

for an aneuploid gene at least as a marker for cancer or preancerous cells or damaged tissue, one skilled in the art would find it entirely reasonable that PRO1112 is useful in the early detection of lung and colon cancer.

(2) The Examiner alleges that the Ashkenazi Declaration actually supports the Examiner's position in that it provides further evidence that gene amplification does not always correlate with increased mRNA/polypeptide levels. First, "always" is not required by the utility standard. Second, this position of the Examiner is based on a complete misinterpretation of the Ashkenazi Declaration, its teachings and the arguments presented by the Appellants regarding this Declaration. Appellants fail to see how the Ashkenazi Declaration could support the Examiner's arguments when Appellants clearly stated that, even if there were no correlation between gene amplification and increased mRNA/protein expression, **(which Appellants expressly do not concede to)**, a polypeptide encoded by a gene that is amplified in cancer would still have a specific, substantial, and credible utility. Appellants submit that, based on the teachings of the Ashkenazi Declaration and the Hanna and Mornin reference (both previously made of record), one of skill in the art would have known that simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, were not to be over-expressed. This leads to better determination of a suitable therapy for the tumor, as demonstrated by a real-world example of the breast cancer marker HER-2/neu. Again, the presentation of this explanation in support of utility is not to be interpreted as a submission of a lack of correlation between DNA and/or mRNA/protein levels.

(3) Appellants have already discussed the references Pennica *et al.*, Konopka *et al.*, Sen *et al.*, Hittelman *et al.*, Fleischhaacker *et al.*, Godbout *et al.*, and Li *et al.* in great detail throughout prosecution and in their Appeal Brief filed April 14, 2008; these discussions and arguments are hereby incorporated by reference.

Briefly, the teachings of Pennica *et al.* are specific to *WISP* genes, a specific class of closely related molecules. Pennica *et al.* showed that there was good correlation between DNA and mRNA expression levels for the *WISP-1* gene but not for *WISP-2* and *WISP-3* genes. The fact that, for two out of three specific molecules there seems to be no correlation between gene

amplification and/or mRNA/protein expression, does not establish that it is more likely than not, in general, that such correlation does not exist. As discussed throughout prosecution, the standard is not absolute certainty. Pennica *et al.* has no teaching whatsoever about the correlation of gene amplification and protein expression for genes in general. Indeed, the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level. In fact, as noted even in Pennica *et al.*, “[a]n analysis of *WISP-1* gene amplification and expression in human colon tumors *showed a correlation between DNA amplification and over-expression . . .*” (Pennica *et al.*, page 14722, left column, first full paragraph, emphasis added). Accordingly, Appellants respectfully submit that Pennica *et al.* teaches nothing conclusive regarding the absence of correlation between gene amplification and over-expression of mRNA or polypeptides in most genes, in general. Therefore, the teachings of Pennica *et al.* are not directed towards genes in general but to a single gene or genes within a single family and thus, their teachings cannot support a general conclusion regarding a correlation between gene amplification and mRNA or protein levels.

Regarding Konopka *et al.*, Applicants submit that the Examiner has completely misinterpreted the statement that “[p]rotein expression is not related to amplification of the *abl* gene but to variation in the level of *bcr-abl* mRNA produced from a single Ph¹ template.” (See Konopka *et al.*, Abstract). Konoka teaches that “[t]he demonstration that the Ph¹ chromosomal template can vary in its level of expression of P210 ^{c-abl} suggests that secondary mechanisms, beyond the translocation itself, contribute to the regulation of the *bcr-abl* gene in different cell types or subclones that derive from the affected stem cell.” (page 4049, 2nd column, 2nd paragraph) In an effort to characterize this differential expression, Konopka examined the production of the *abl* RNA via RNA blot hybridization analysis (Fig. 3), which “showed that the normal 6- and 7-kb *c-abl* mRNAs were present at a similar level in Ph¹-positive and -negative cell lines derived from different patients.” (page 4050, 2nd column, last paragraph) However, Konopka found that “the 8-kb mRNA that encodes P210 ^{c-abl} was detected at a 10-fold higher level in SK-CML7Bt-33 (Fig. 3A, +) than in SK-CML16Bt-1 (B, +), which correlated with the relative level of P210 ^{c-abl} detected in each cell line. Analysis of additional cell lines demonstrated that the level of 8-kb RNA directly correlated with the level of P210 ^{c-abl} (Table 1)” (page 4050, 2nd column, last paragraph; underlining added). As a further control, Konopka

looked at DNA levels and found that "[t]he variation in level of 8-kb RNA detected in these cell lines was not due to loss or gain of Ph¹, because cytogenetic analysis confirmed the presence of Ph¹ in these cell lines." (page 4050, 2nd column, last paragraph) Konopka further established that "[t]here was no difference in the copy number of abl-related sequences as judged by Southern blot analysis (Fig. 4)." (page 4051, 1st column) From this study, Kopoka concludes "[t]hese combined data suggest that differential bcr-abl mRNA expression from a single gene template is responsible for the variable levels of P210 ^{c-abl} detected." (page 4051, 1st column) Therefore, the teachings of Konopka *et al.* are not pertinent to the examiner's argument because they are not directed towards the correlation of gene amplification and its gene product other than to demonstrate that there are mechanisms other than gene amplification that contribute to protein overexpression in cancer. However, Kopoka does support Applicants' position regarding a correlation between mRNA and protein levels.

The Examiner has asserted that "Hanna *et al.* supports the rejection, in that Hanna *et al.* show that gene amplification does not reliably correlate with protein over-expression, and thus the level of polypeptide expression must be tested empirically." (Page 30 of the Examiner's answer). Appellants respectfully reiterate that the Examiner appears to have misread Hanna *et al.* Hanna *et al.* clearly state that gene amplification (as measured by FISH) and polypeptide expression (as measured by immunohistochemistry, IHC) are well correlated ("in general, FISH and IHC results correlate well" (Hanna *et al.* p. 1, col. 2)). It is only a subset of tumors which show discordant results. Thus Hanna *et al.* support Appellants' position that it is more likely than not that gene amplification correlates with increased polypeptide expression.

In contrast, in the majority of amplified genes, the teachings in the art, as exemplified by Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Appellants submit that when the proper legal standard is applied, one of skill in the art should reach the conclusion, based on the amplification data for the PRO1112 gene, that the PRO1112 polypeptide is concomitantly overexpressed, and that the present application discloses at least one patentable utility for the claimed PRO1112 polypeptides. Accordingly, one of ordinary skill in the art would also understand how to make and use the recited polypeptides for the diagnosis of lung and colon cancer without any undue experimentation.

The Examiner contends that the Li article constitutes strong opposing evidence for the presumption that the claimed polypeptides are also overexpressed following gene amplification. Appellants respectfully disagree. The Li article was discussed extensively in the Appeal Brief filed April 14, 2008; these discussions and arguments are hereby incorporated by reference. In the article, genes were considered to be amplified if they had a copy number ratio of at least 1.40. In the instant case for PRO1112, as discussed in the Goddard Declaration (of record), an appropriate threshold for considering gene amplification to be significant is a copy number of at least 2.0 (which is a higher threshold than Li's 1.40). The PRO1112 gene showed significant amplification of **2.092 – 4.807 fold amplification in twelve different colon tumors and 2.196 – 3.364 fold amplification in seven lung tumors**, and thus fully meets the Goddard standard as well as the Li standard. Appellants further note, and it is not surprising that, in the Li *et al.* reference, by using a lower threshold of 1.4 for considering gene amplification, a higher number of genes not showing corresponding increases in mRNA expression were found. Nevertheless, the results of Li *et al.* do not conclusively disprove that a gene with a substantially higher level of gene amplification, such as PRO1112, would be expected to show a corresponding increase in transcript expression. Therefore Li does not constitute opposing evidence.

In response to Applicants' argument that the discordance may reflect methodologic differences, the Examiner asserts that "Li *et al.* did not limit their studies to genes that were amplified at less than 2-fold." In support of this assertion, the Examiner cites the first paragraph of the Supplemental Material. (Page 25 of the Examiner's Answer). Applicants respectfully point out that the Examiner has misinterpreted the Li *et al.* methodology disclosed in the supplemental material. The evidence cited by the Examiner pertains to the inclusion criteria of the probes used for defining amplicons. In the second paragraph entitled "Relationship between genomic copy number and gene transcript level", the authors state that "[f]or each gene, the CGH data were represented by a vector that was labeled '1' for genomic overrepresentation (including amplification) ratio greater than 1.40 and '0' for no genomic overrepresentation." Nevertheless, the Examiner acknowledges that the alleged 2-fold amplification criteria would only apply to some of the samples examined by Li *et al.* The Examiner has not established that a correlation does not exist in samples based solely on this threshold.

Based on Godbout et al., the Examiner asserts “that the protein encoded by the PRO1112 gene would confer any selective advantage on a cell expressing it” in the Examiner’s answer; in other words, the Examiner requests Appellants to show the mechanism by which the claimed protein acts within the cell. However, Appellants respectfully remind the Board that demonstration of the mechanism is not a requirement for attaining that utility. Appellants believe that such a requirement is a heightened utility standard imposed by the Examiner. In fact, as stated by the Federal Circuit, “it is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works.” *In re Cortwright*, 165 F.2d 1353, 1359 (Fed. Cir. 1999). The Federal Circuit has also stated that “[a]n invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: “[T]he fact that an invention has only limited utility and is not operable in certain applications is not grounds for finding lack of utility.” *Envirotech Corp. v. Al George, Inc.* 730 F.2d 753, 762, 221 USPQ 473,480 (Fed. Cir. 1984).” Hence this rejection is improper.

(4) The Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* references were presented during prosecution to show that, in general, gene amplification increases mRNA expression. As Appellants have acknowledged, the correlation between changes in mRNA level and protein level is not exact, and there are exceptions. However, Appellants have submitted during prosecution over 100 references in addition to the declarations and references already of record which support Appellants’ asserted utility, either directly or indirectly. This included references that studied single genes or gene families, multiple or large families of genes, and included studies that a wide variety of techniques, including gene amplification and microarray. Regardless of the techniques employed, by and large, increased gene levels generally correlated well with increased mRNA and /or protein levels, even if accurate predictions of proteins could not be made. As discussed throughout prosecution, the law does not require the existence of a “necessary” correlation between DNA/mRNA and protein levels, or that protein levels be “accurately predicted.” In fact, authors in several of the cited references (cited both, by the Examiner, and by Appellants) themselves acknowledge that there is a general correlation between protein expression and transcript levels and DNA levels, which meets the “more likely than not standard.” Therefore Appellants have explored this issue thoroughly throughout

prosecution in the vast number of references presented in this case and the evidence should be viewed as a whole.

Regarding the Examiner's contention that references Orntoft *et al.*, Hyman *et al.*, Pollack *et al.* are flawed because, allegedly, their studies were directed to highly amplified genes or abundant proteins, Appellants have submitted that PRO1112 is significantly amplified (according to the Goddard Declaration) throughout prosecution. Appellants believe that this significantly amplified DNA would more likely than not result in a higher expression of PRO1112 protein, according to the teachings of many references including Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.*.

Collectively, Appellants submit that the Examiner's concerns in this rejection are misplaced and cannot properly form the basis for utility rejections of the present claims.

II. *Claim Rejections Under 35 U.S.C. §112, First Paragraph - Enablement*

Claims 119-126 and 129-131 stand rejected under 35 U.S.C. §112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains or with which it is most nearly connected, to make and/or use the invention.

Appellants disagree for the reasons previously presented in Appellants Brief and in the discussion presented herein under Claim Rejections under 35 USC §101. Appellants submit that, as discussed above, the PRO1112 polypeptides have utility in the diagnosis of lung and colon cancers. Based on such a utility, one of skill in the art would know exactly how to use the claimed polypeptides, for example, for diagnosis of cancer without any undue experimentation.

III. *Claim Rejections Under 35 U.S.C. §112, First Paragraph – Written Description*

Claims 119-123, 130 and 131 stand rejected under 35 U.S.C. §112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Appellants disagree for the reasons previously presented in Appellants Brief filed April 14, 2008. Appellants maintain that, based on the ample disclosure in the specification, one

skilled in the art would have known that Appellants had knowledge and possessed the claimed polypeptides with 80-99% sequence identity to SEQ ID NO: 207 whose encoding nucleic acids were amplified in colon and lung tumors. The recited property of amplification of the encoding gene adds to the characterization of the claimed polypeptide sequences in a manner that one of skill in the art could readily assess and understand. As discussed previously, Appellants have recited structural features, namely 80-99% sequence identity to SEQ ID NO: 207, which are common to the genus. Appellants have also provided guidance as to how to make the recited variants of SEQ ID NO: 207, including listings of exemplary and preferred sequence substitutions. The genus of claimed polypeptides is further defined by having a specific functional activity for the encoding nucleic acids. Accordingly, a description of the claimed genus has been achieved.

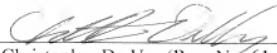
CONCLUSION

For the reasons given above, Appellants submit that the present specification clearly describes, details and provides a patentable utility for the claimed invention. Moreover, it is respectfully submitted that based upon this disclosed patentable utility, the present specification clearly teaches "how to use" the presently claimed polypeptide and provides an adequate written description of the claimed genus. As such, Appellants respectfully request reconsideration and reversal of the outstanding rejections of Claims 119-126 and 129-131.

The Commissioner is authorized to charge any fees which may be required, including extension fees, or credit any overpayment to Deposit Account No. 07-1700 (referencing Attorney's Docket No. 123851-181895 (GNE-2730 PIC13)).

Respectfully submitted,

Date: August 12, 2008

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